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Trimethylsilyl Trifluoromethanesulfonate (TMSOTf) Assisted Facile Deprotection of *N,O*-Acetonides

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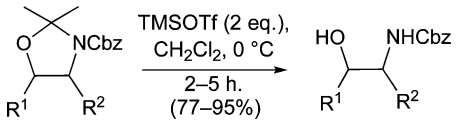
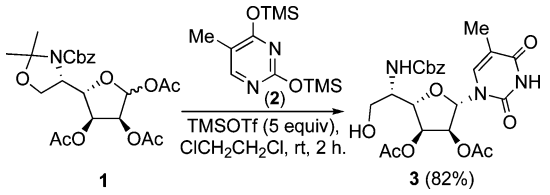


Employing TMSOTf as an easily available reagent, we have developed a mild and efficient method for the deprotection of both terminal and internal *N,O*-acetonide functionalities. Various regularly used protecting groups and common organic functional moieties were found to be unaffected by the described reaction conditions. In a few representative examples, the present method was also extended to deprotect acetonides obtained from 1,2-, and 1,3-terminal diols. The acetonide deprotection protocol described herein is expected to be a useful addition to the presently available methods for performing the above transformation.

Isopropylidene ketal (acetonide) formation is among the most frequently used protocols for the simultaneous protection of 1,2- or 1,3-diols and aminoalcohols.[1] Consequently, development of methods for such acetonide-forming reactions and selective removal of these protecting groups continues to be an active area of research.[1−3] The classical methods for both the formation and deprotection of acetonides generally involve the presence of either a protic or a Lewis acid catalyst.[1] In recent unrelated research in our laboratory, while attempting a nucleoside-forming reaction involving the C4′-*N,O*-acetonide-containing glycosyl donor **1** (Scheme 1) and bis-silylated thymine (**2**), in the presence of an excess of TMSOTf as the activator (Vorbrüggen protocol),[4] we found that, in addition to the desired nucleobase incorporation, the Lewis acidic reaction condition has also resulted in clean cleavage of the acetonide protection to form the corresponding nucleoside derivative **3** in high yield. It is worth mentioning that the only known instances of acetonide functionality cleavage in the presence of silyl triflates have been reported by Rychnovsky and co-workers during the early 1990s.[5,6] In their studies aimed at "protecting group interconversion", acetonides derived from 1,2- or 1,3-terminal diols on treatment with TMSOTf or TESOTf in the presence of Hünig's base were found to regioselectively rearrange to acetonide-cleaved products, with concomitant reprotection of the resulting primary hydroxy group as its silylether and the secondary hydroxy group as an isopropenyl ether. Interestingly, internal acetonides remained unaffected under the above conditions, thereby also providing an efficient protocol to differentiate terminal acetonides from internal ones (Figure 1).[6]

SCHEME 1



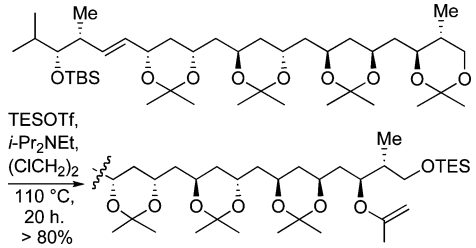


FIGURE 1. Rychnovsky's acetonide interconversion protocol.[5b]

To the best of our knowledge, there have been no reports on *N,O*-acetonide deprotection utilizing silyl triflates. Intrigued by the observation from our nucleoside-forming reaction above (Scheme 1) and Rychnovsky's studies on diol acetonides, we decided to further investigate the possibility of TMSOTf-assisted deprotection of *N,O*-acetonides. The details of the studies undertaken are reported herein.

In an initial reaction, the L-serinol-derived *N,O*-acetonide **4a** (Scheme 2) was treated with 2 equiv of TMSOTf, and the reaction mixture was stirred at 0 °C for 2 h. Subsequent quenching of the reaction by the addition of an aqueous saturated sodium bicarbonate solution followed by column chromatographic purification of the crude product provided the desired

(1) Wuts, P. G. M.; Greene, T. W. *Greene's Protective Groups in Organic Synthesis*, 4th ed.; John Wiley & Sons: New Jersey, 2007.

(2) For some recent studies on the deprotection of *O,O*-acetonides, see: (a) Coste, G.; Gerber-Lemaire, S. *Tetrahedron Lett.* **2006**, *47*, 671−674. (b) Sabitha, G.; Reddy, G. S. K. K.; Reddy, K. B.; Reddy, N. M.; Yadav, J. S. *J. Mol. Catal. A* **2005**, *238*, 229−232. (c) Reddy, S. M.; Reddy, Y. V.; Venkateswarlu, Y. *Tetrahedron Lett.* **2005**, *46*, 7439−7441. (d) Yadav, J. S.; Satyanarayana, M.; Raghavendra, S.; Balanarsaiah, E. *Tetrahedron Lett*. **2005**, *46*, 8745−8748. (e) Chari, M. A.; Syamasundar, K. *Synthesis* **2005**, 708−710 and references therein.

(3) For some recent reports on the deprotection of *N,O*-acetonides, see: (a) Cong, X.; Hu, F.; Liu, K.-G.; Liao, Q.-J.; Yao, Z.-J. *J. Org. Chem.* **2005**, *70*, 4514−4516. (b) Shaikh, N. S.; Bhor, S. S.; Gajare, A. S.; Deshpande, V. H.; Wakharkar, R. D. *Tetrahedron Lett.* **2004**, *45*, 5395−5398 and references therein.

(4) For a review, see: Vorbrüggen, H.; Ruh-Pohlenz, C. *Org. React.* **2000**, *55*, 1−630.

(5) (a) Rychnovsky, S. D.; Kim, J. *Tetrahedron Lett*. **1991**, *32*, 7219−7222. (b) Rychnovsky, S. D.; Hoye, R. C. *J. Am. Chem. Soc*. **1994**, *116*, 1753−1765.

(6) We are thankful to one of the reviewers of this manuscript for bringing to our attention the following publication, observing the cleavage of an *O,O*-acetonide (albeit as a minor reaction), presumably by TMSOTf. Procopiou, P. A.; Lynn, S. M.; Roberts, A. D. *Tetrahedron* **1999**, *55*, 3649−3656.

10.1021/jo7021923 CCC: $40.75
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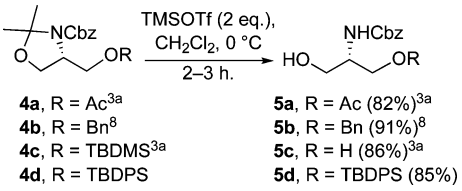
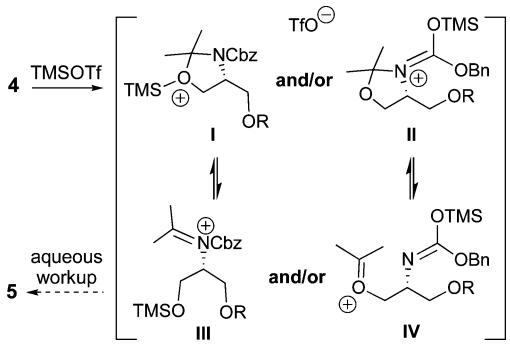
SCHEME 2



acetonide-deprotected aminoalcohol **5a** in good yield. The acetyl protecting group of **4a** was found to be stable to the above reaction conditions.

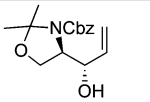
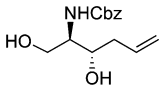
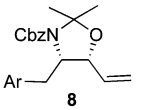
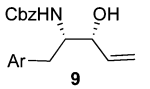
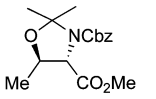
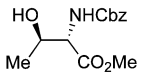
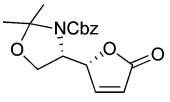
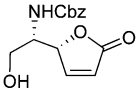
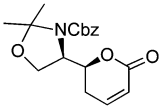
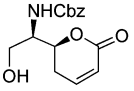
A probable mechanistic pathway for the observed acetonide cleavage is proposed in Scheme 3.[7] Initial complexation of the oxazolidine ring oxygen and/or the carbamoyl oxygen by the Lewis acidic TMSOTf results in the formation of the activated cationic species **I** and/or **II** and their subsequent rearranged products **III**/**IV**. Aqueous workup of the reaction mixture then leads to the acetonide-deprotected product **5** (Scheme 3). Unlike in Rychnovsky's method,[5] the absence of any base in the reaction presumably prevents the base-induced rearrangement of the activated acetonide, thereby avoiding the enol ether (as in Figure 1) formation.

SCHEME 3



With an aim to explore the compatibility of the present acetonide cleavage protocol with other commonly used protecting groups, variously protected *N*,*O*-acetonides were then subjected to the above TMS-assisted deprotection reaction. Thus, the benzyl ether moiety of **4b** (Scheme 2) was found to be unaffected by the described reaction conditions, providing the corresponding *N*-Cbz-aminoalcohol derivative **5b** in high yield. On the other hand, the *tert*-butyldimethylsilyl (TBDMS) ether functionality of the acetonide **4c** was found to be unstable to the above conditions, leading to cleavage of both the *N*,*O*-acetonide and TBDMS ether linkages to form the amino diol **5c** in high yield. The observed desilylation reaction is not completely unexpected, as TBDMS ethers are known to be deprotected by TMSOTf.[1,9] In contrast, the *tert*-butyldiphenylsilyl (TBDPS) protecting group of the *N*,*O*-acetonide **4d** was found to be stable to TMSOTf, and the desired acetonide-deprotected product **5d** was obtained in 85% yield (Scheme 2). In further exploration of the method, several other *N*,*O*-acetonides were also subjected to successful deprotection employing the present acetonide cleavage protocol (Table 1). Thus, the aminodiol derivative **7** could be easily obtained by deprotection of the corresponding acetonide **6**. More interestingly, the internal *N*,*O*-acetonide protection of the substrates **8** and **10** could also be efficiently cleaved to provide the corresponding aminoalcohol derivatives **9** and **11**, respectively (Table 1). The deprotections were equally facile with both the *cis*-**8**- and *trans*-**10**-substituted acetonides. It is worth noting that both the ester functionality and the stereochemical integrity of **10** remained unaffected under the acetonide deprotection conditions. When extended toward deprotection of the acetonide functionalities as present in the chiral α,β-unsaturated lactones **12** and **14**, the desired aminoalcohols **13** and **15** were obtained in very high yields. The strategically functionalized lactones **12** and **14** are routinely used as key synthetic intermediates in several ongoing research projects in our group. In our hands, the present deprotection protocol was found to be more efficient and better yielding compared to some of the literature reported acetonide deprotection methods (e.g., aq AcOH, HCO_2H, PTSA/MeOH, DOWEX (H^+) resin/MeOH, etc.) previously employed by us to perform the same transformation. One of the limitations of the present method is the instability of the *N*-Boc functionality to TMSOTf, thus the method is not suitable for substrates containing *N*-Boc-protected *N*,*O*-acetonides.[14]

TABLE 1. TMSOTf-Assisted Deprotection of *N*,*O*-Acetonides

Starting material	Product	Reaction time (yield %)
 **6** (Ref. 10)	 **7** (Ref. 10)	2.5 h (77%)
 **8** (Ar = 4-$MeOC_6H_4$)	 **9** (Ar = 4-$MeOC_6H_4$)	5 h (92%)
 **10** (Ref. 11)	 **11** (Ref. 11)	4 h (95%)
 **12** (Ref. 12)	 **13** (Ref. 13)	3 h (91%)
 **14** (Ref. 12)	 **15**	2 h (94%)

(7) We thank one of the reviewers of this manuscript for suggesting an alternative mechanistic pathway (via the formation of **II** and **IV**, Scheme 3) leading to the observed acetonide cleavage.

(8) Delle Monache, G.; Di Giovanni, M. C.; Maggio, F.; Misiti, D.; Zappia, G. *Synthesis* **1995**, 1155−1158.

(9) (a) Hunter, R.; Hinz, W.; Richards, P. *Tetrahedron Lett.* **1999**, *40*, 3643−3646. (b) Bou, V.; Vilarrasa, J. *Tetrahedron Lett.* **1990**, *31*, 567−568.

(10) Khalaf, J. K.; Datta, A. *J. Org. Chem.* **2004**, *69*, 387−390.

(11) Evans, D. A.; Hu, E.; Tedrow, J. S. *Org. Lett.* **2001**, *3*, 3133−3136.

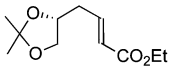
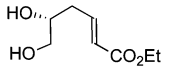
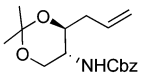
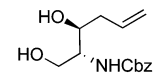
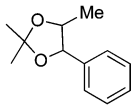
(12) Bhaket, P.; Stauffer, C. S.; Datta, A. *J. Org. Chem.* **2004**, *69*, 8594−8601.

(13) Bhaket, P.; Morris, K.; Stauffer, C. S.; Datta, A. *Org. Lett.* **2005**, *7*, 875−876.

(14) For examples of Boc deprotection (in *N*-Boc compounds) with TMSOTf and TBDMSOTF, see ref 1.

(15) Labelle, M.; Morton, H. E.; Guindon, Y.; Springer, J. P. *J. Am. Chem. Soc.* **1988**, *110*, 4533−4540.

TABLE 2. Studies on TMSOTf-Assisted Deprotection of *O,O*-Acetonides

Starting material	Product	Reaction time (yield %)
 **16** (Ref. 15)	 **17** (Ref. 15)	4 h (90%)
 **18** (Ref. 10)	 **19** (Ref. 10)	5 h (79%)
 **20** (Ref. 16)	Recovered s.m., or, complex mixture of products	1–6 h

Having successfully demonstrated the TMSOTf-assisted deprotection of various *N,O*-acetonides, we decided to investigate the feasibility of the above protocol in the deprotection of *O,O*-acetonides. Accordingly, in a subsequent study, a representative set of 1,2- and 1,3-diol-derived *O,O*-acetonides **16**, **18**, and **20** (Table 2) was subjected to deprotection in the presence of TMSOTf. Thus, the 1,2-diol acetonide **16** on treatment with TMSOTf under similar conditions as described earlier provided the corresponding free diol **17** (Table 2) in 90% yield. The reaction was equally successful when extended to the corresponding 1,3-diol-derived acetonide **18**, resulting in the deprotected 1,3-diol **19** in good yield. However, in conformity with Rychnovsky's observations,[5] the acetonide **20**, derived from two secondary hydroxyl groups, failed to undergo acetonide deprotection under the above conditions.

The structures and stereochemical purity (as applicable) of all the products obtained during the present studies were confirmed by their spectral and analytical data and by comparison with known compounds wherever available.

In conclusion, employing TMSOTf as an easily available reagent, we have developed a mild and efficient method for the deprotection of both terminal and internal *N,O*-acetonide functionalities. A variety of other types of protecting groups and common functional moieties were found to be unaffected by the described reaction conditions, thereby adding to the utility of the method. Complementary to the terminal *O,O*-acetonide deprotection method as developed by Rychnovsky, in a few selected examples, the present method was also found to deprotect acetonides formed from 1,2- and 1,3-terminal diols. We hope that the acetonide deprotection protocol described herein will prove to be a useful addition to the literature methods for acetonide deprotection and will also provide an alternative protocol to the known methods.

Experimental Section

Compound 3. To a solution of the triacetate **1**[12] (1 g, 2.09 mmol) in anhydrous $(CH_2Cl)_2$ (25 mL) were added sequentially bis-(trimethylsilyl)thymine (1.41 g, 5.21 mmol, 2.5 equiv) and TMSOTf (1.9 mL, 10.43 mmol, 5 equiv). After stirring at room temperature for 2 h, the reaction was quenched by the addition of saturated aqueous $NaHCO_3$ solution (10 mL). The organic layer was separated, and the aqueous layer was extracted with $CHCl_3$ (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4, and concentrated under vacuum, and the residue was purified by flash chromatography (EtOAc/hexanes = 3/2 to 4/1) to yield pure **3** (870 mg, 82%) as a foamy semisolid: $[\alpha]^{25}_D$ −4.0 (*c* 1, $CHCl_3$); IR (neat) broad 3306, 1751, 1747, 1693 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.90 (s, 3H), 2.09 (s, 6H), 2.65 (br s, 1H, exchangeable with D_2O), 3.70−3.78 (m, 1H), 3.92−4.0 (m, 1H), 4.05−4.22 (m, 1H), 4.31−4.39 (m, 1H), 5.13−5.14 (m, 2H), 5.34−5.37 (m, 1H), 5.48−5.51 (m, 1H), 5.63 (br s, 1H), 5.79 (d, *J* = 5.5 Hz, 1H), 7.08 (s, 1H), 7.33−7.46 (m, 5H), 8.37 (s, 1H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 12.8, 20.8, 20.9, 53.9, 61.8, 67.5, 71.2, 72.9, 81.9, 89.4, 112.3, 128.5, 128.6, 128.9, 136.6, 137.1, 151.2, 157.1, 164.2, 170.3, 170.5; HRMS (*m/z*) calcd for $C_{23}H_{28}N_3O_{10}$ (M + H) 506.1775, found 506.1764.

General Procedure for TMSOTF-Assisted Acetonide Deprotection. To a stirred, ice-cold solution of the acetonide derivative in anhydrous CH_2Cl_2 (10% solution w/v) under an inert atmosphere was added TMSOTf (2 equiv) through a syringe. The resulting solution was stirred at the same temperature for the specified time (TLC monitoring), followed by quenching the reaction by addition of a saturated aqueous $NaHCO_3$ solution. After stirring the mixture for 5 min, the organic layer was separated and the aqueous layer was saturated with solid NaCl and extracted with CH_2Cl_2 (three times). The combined organic layers were dried over anhydrous Na_2SO_4. Concentration of the solvent under reduced pressure and column chromatographic purification of the residue provided the pure acetonide-cleaved product.

Compound 4d. Colorless oil; $[\alpha]_D$ −20.7 (*c* 0.56, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz, mixture of rotamers) δ 7.70−7.62 (m, 4H), 7.47−7.21 (m, 11H), 5.19−4.96 (m, 2H), 4.26−3.81 (3m, 4H), 3.69−3.55 (m, 1H), 1.57−1.15 (4s, 6H), 1.09 and 1.06 (2s, 9H); ^{13}C NMR ($CDCl_3$, 125.7 MHz, mixture of rotamers) δ 152.9, 152.2, 136.2, 135.6, 135.5, 133.6, 133.4, 133.3, 129.8, 128.5, 128.1, 128.0, 127.9, 127.8, 127.7, 94.3, 93.9, 67.2, 66.5, 65.4, 65.1, 62.9, 62.3, 58.9, 58.1, 27.4, 26.9, 26.8, 26.5, 24.6, 23.1, 19.3, 19.2; HRMS (ESI, *m/z*) calcd for $C_{30}H_{38}NO_4Si$ ($M + H^+$) 504.2570, found 504.2548.

Compound 5d. Low-melting solid; $[\alpha]_D$ 1.8 (*c* 1.02, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.53−7.50 (m, 4H), 7.35−7.22 (m, 11H), 5.20 (br s, 1H), 4.99 (s, 2H), 3.74−3.59 (m, 5H), 2.12 (br s, 1H), 0.95 (s, 9H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 156.5, 136.4, 135.5, 132.7, 130.0, 128.6, 128.2, 128.1, 127.9, 66.9, 64.1, 63.4, 53.3, 26.9, 19.2; HRMS (ESI, *m/z*) calcd for $C_{27}H_{34}NO_4Si$ ($M + H^+$) 464.2257, found 464.2278.

Compound 8. Colorless liquid; $[\alpha]_D$ −11.4 (*c* 0.51, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz, mixture of rotamers) δ 7.43−7.35 (m, 5H), 7.05−6.99 (m, 2H), 6.81−6.78 (m, 2H), 5.78−5.72 (m, 1H), 5.20−5.14 (m, 4H), 4.36 (br s, 1H), 3.93 (br s, 1H), 3.80 (s, 3H), 3.05−3.01 (m, 2H), 1.68 and 1.63 (2s, 3H), 1.29 and 1.20 (2s, 3H); ^{13}C NMR ($CDCl_3$, 125.7 MHz, mixture of rotamers) δ 158.3, 152.3, 136.9, 136.4, 131.0, 130.6, 129.1, 128.6, 128.2, 117.7, 113.8, 95.7, 95.3, 79.2, 78.7, 67.0, 63.4, 63.0, 55.2, 37.7, 35.1, 29.1, 27.2, 26.5, 25.0; HRMS MS (ESI, *m/z*) calcd for $C_{23}H_{28}NO_4$ ($M + H^+$) 382.2018, found 382.2023.

Compound 9. White solid; mp 117−118 °C; $[\alpha]_D$ 58.3 (*c* 1.01, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.27−7.23 (m, 5H), 7.07 (d, *J* = 10 Hz, 2H), 6.75 (d, *J* = 10 Hz, 2H), 5.84−5.77 (m, 1H), 5.19 (d, *J* = 17 Hz, 1H), 5.10 (d, *J* = 10.5 Hz, 1H), 5.11−4.96 (m, 3H), 4.06 (s, 1H), 3.79 (d, *J* = 5 Hz, 1H), 3.71 (s, 3H), 2.84−2.24 (m, 2H), 2.04 (s, 1H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 158.3, 156.5, 138.2, 136.5, 130.3, 130.0, 128.5, 128.1, 127.9, 116.3, 114.0, 72.4, 66.7, 56.4, 55.3, 37.1; HRMS (ESI, *m/z*) calcd for $C_{20}H_{24}NO_4Na$ ($M + Na^+$) 364.1525, found 364.1542.

Compound 15. White solid; mp 85−87 °C; $[\alpha]_D$ −40.7 (*c* 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.26−7.24 (m, 5H), 6.86−6.83 (m, 1H), 5.94 (d, *J* = 9.5 Hz, 1H), 5.53 (d, *J* = 8.5 Hz, 1H), 5.04 (s, 2H), 4.50−4.45 (m, 1H), 4.0 (d, *J* = 10.5 Hz, 1H), 3.85 (br s, 1H), 3.68 (d, *J* = 10 Hz, 1H), 2.56−2.36 (m, 3H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 163.8, 156.4, 145.8, 136.1, 128.6, 128.3,

(16) Bovicelli, P.; Sanetti, A.; Lupattelli, P. *Tetrahedron* **1996**, *52*, 10969−10978 and references therein.

128.1, 121.0, 67.2, 60.5, 55.0, 54.4, 26.5; HRMS (ESI, *m/z*) calcd for $C_{15}H_{18}NO_5$ ($M + H^+$) 292.1185, found 292.1174.

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Supporting Information Available: General experimental procedure and copies of NMR spectra (^1H and ^{13}C) of all the new compounds synthesized. This material is available free of charge via the Internet at http://pubs.acs.org.

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